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Recipient female gender is a risk factor for graft loss after liver transplantation for chronic hepatitis C: Evidence from the prospective Liver Match cohort

Luca Saverio Belli[a,*], Renato Romagnoli[b], Alessandra Nardi[c], Tania Marianelli[c], Francesca Donato[d], Stefano Ginanni Corradini[e], Rosa Maria Iemmolo[f], Cristina Morelli[g], Luisa Pasulo[h], Maria Rendina[i], Eleonora De Martin[j], Francesca Romana Ponziani[k], Riccardo Volpes[l], Mario Strazzabosco[m], Mario Angelico[n], Liver Match Investigators

[a] Department of Hepatology and Gastroenterology, Niguarda Hospital, Milan, Italy
[b] Liver Transplant Center, Azienda Ospedaliera Città della Salute e della Scienza, University of Turin, Italy
[c] Department of Mathematics, Tor Vergata University Hospital, Rome, Italy
[d] Division of Digestive Diseases, "Maggiore" University Hospital, Milan, Italy
[e] Division of Gastroenterology, Sapienza University, Rome, Italy
[f] Liver Transplant Center, University Hospital, Modena, Italy
[g] Liver Transplant Center, University Hospital, Bologna, Italy
[h] Gastroenterology and Transplant Hepatology, San Giovanni XXIII Hospital, Bergamo, Italy
[i] Department of Emergency and Organ Transplantation, University Hospital, Bari, Italy
[j] Liver Transplant Center, University Hospital, Padua, Italy
[k] Department of Internal Medicine and Gastroenterology, Gemelli Hospital, Rome, Italy
[l] Mediterranean Institute for Transplant, Palermo, Italy
[m] Digestive Disease Section, University Hospital Milano Bicocca and Yale University Center, New Haven, USA
[n] Hepatology Unit, Tor Vergata University, Rome, Italy

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ABSTRACT

Background: Female gender has been reported to be a risk factor for graft loss after liver transplantation for hepatitis C virus (HCV)-related cirrhosis but evidence is limited to retrospective studies.
Aims: To investigate the impact of recipient gender and donor/recipient gender mismatch on graft outcome.
Methods: We performed a survival analysis of a cohort of 1530 first adult transplants enrolled consecutively in Italy between 2007 and 2009 and followed prospectively. After excluding possible confounding factors (fulminant hepatitis, human immunodeficiency virus co-infection, non-viremic anti-HCV positive subjects), a total of 1394 transplant recipients (604 HCV-positive and 790 HCV-negative) were included.
Results: Five-year graft survival was significantly reduced in HCV-positive patients (64% vs 76%, $p = 0.0002$); Cox analysis identified recipient female gender (HR = 1.44, 95% CI 1.03–2.00, $p = 0.0319$), Mayo clinic End stage Liver Disease score (every 10 units, HR = 1.25, 95% CI 1.03–1.50; $p = 0.022$), portal thrombosis (HR = 2.40, 95% CI 1.20–4.79, $p = 0.0134$) and donor age (every 10 years, HR = 1.14, 95% CI 1.05–1.24, $p = 0.0024$) as independent determinants of graft loss. All additional mortality observed among female recipients was attributable to severe HCV recurrence. Conclusions. This study unequivocally shows that recipient female gender unfavourably affects the outcome of HCV-infected liver grafts.

1. Introduction

Donor and recipient factors influence the outcome of liver transplantation (LT) in individuals infected with hepatitis C virus (HCV). Some of the risk factors, such as donor age and Model for End-stage Liver Disease (MELD) score, are well-established [1]. The role of gender as a risk factor for graft loss after LT remains unclear, and

* Corresponding author at: Department of Hepatology and Gastroenterology, Niguarda Hospital, Piazza Ospedale Maggiore 3, 20162 Milan. Italy. Tel.: +39 02 6444 4436; fax: +39 02 6444 2788.
E-mail address: luca.belli@ospedaleniguarda.it (L.S. Belli).

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evidence is limited to retrospective studies, suggesting that, in anti-HCV-positive recipients, the risk for graft loss is increased in female recipients.

Natural history studies of HCV infection show that chronic liver disease progresses at unequal rates between women and men, as women experience a slower rate of fibrosis progression per year [2] and a lower incidence of end-stage liver disease compared to men [3]. Quite surprisingly, recipient gender seems to play an opposite role in the transplant setting, with at least two retrospective studies reporting that female gender is a risk factor for a rapidly progressive HCV recurrence after LT [4,5]. A large retrospective study [6] showed that anti-HCV-positive female recipients have an increased risk of graft failure only when they receive a graft from a male donor. This finding has not been confirmed in other retrospective studies, and it has not been tested prospectively and against other relevant covariates.

The Liver Match is a prospective observational cohort including 1530 consecutive first transplants performed in adult recipients in Italy between June 2007 and May 2009 for which detailed baseline and follow-up information regarding both donors and recipients have been prospectively recorded [7]. This Italian cohort is therefore optimally suited for a prospective assessment of the role of gender, donor/recipient gender mismatch and other donor/recipient covariates on graft outcome, particularly in the subgroup of recipients in whom the liver graft undergoes HCV reinfection because of detectable HCV-RNA in serum at the time of LT [8].

2. Patients and methods

2.1. Patient population and recorded variables

Twenty transplant centres, representing approximately 90% of the whole adult liver transplantation activity performed in Italy, agreed to participate to the data collection through the recruitment of 1530 adult first transplants from deceased heart-beating donors performed between June 1, 2007 and May 31, 2009. Baseline data regarding donor and recipient, the various steps of organ procurement/allocation and follow-up data were recorded prospectively, as already described in detail [7].

2.1.1. Donor data

The donor data relevant to this study were age, gender, cause of death, cold ischaemia time (CIT), body mass index (BMI), height, history of diabetes mellitus, positivity for anti-hepatitis B core antigen antibodies (anti-HBc), donor risk index (DRI) [9], serum sodium and split liver.

2.1.2. Recipient data at liver transplantation

The following recipient data were recorded at the time of LT: age, gender, donor/recipient sex mismatch, aetiology of liver disease, BMI, presence of hepatocellular carcinoma (HCC) within or outside the Milan criteria, MELD score, sodium, INR, creatinine, bilirubin, previous upper abdominal surgery, presence of complete portal vein thrombosis, insulin dependent diabetes mellitus (IDDM), positivity for anti-HCV antibodies, serum HCV-RNA positivity and HCV genotype. For serum HCV-RNA detection, real time PCR techniques were available in all centres with lower detection limits ranging between 8 and 25 IU/mL.

2.1.3. Post-liver transplant characteristics

The following variables were also recorded after LT: maintenance main immunosuppressant (cyclosporine A, tacrolimus, or other drug), acute rejection episodes requiring additional treatment, serum HCV-RNA positivity within the first 6 months after LT, antiviral treatment with peg-interferon alpha and ribavirin, achievement of a sustained virological response (SVR), HCV-related or unrelated graft loss. Causes of graft loss were recorded according to the European Liver Transplant Registry (ELTR) definitions.

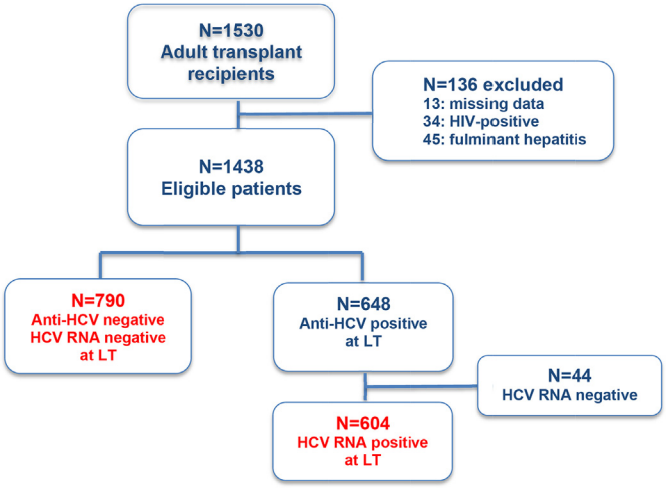

Fig. 1. Flow chart of patient disposition, including first consecutive adult liver transplant recipients from the Liver Match cohort. HCV, hepatitis C virus; LT, liver transplantation; HIV, human immunodeficiency virus.

All follow-up data were recorded prospectively, using detailed web-based forms every 3–6 months during the first year and yearly thereafter. The present analysis included follow-up data recorded until December 31, 2013, with a median follow-up after LT of 51 months for surviving grafts.

2.2. Patient selection criteria

Out of the 1530 LT cases, essential data regarding donor/recipient features and/or follow-up were missing in 13 cases only (0.8%). Patients transplanted for fulminant hepatic failure (FHF, $n = 45$, 2.9%) and patients infected with human immunodeficiency virus (HIV, $n = 34$, 2.3%) were excluded from the analysis. The former were excluded since FHF patients are transplanted in a situation of urgency, which virtually precludes the possibility of donor/recipient matching. Moreover, FHF is known to entail per se a markedly increased risk of early graft failure. Conversely, HIV-positive recipients were excluded since their peri- and post-LT management is complex, requiring the use of anti-HIV drugs; in Italy, these patients may receive an organ only under a strict, still experimental, protocol.

Of the remaining 1438 adult recipients, 790 were anti-HCV negative and 648 anti-HCV positive at the time of LT. In the latter group, 44 patients without active HCV replication, based on undetectable serum HCV-RNA both at LT and in the post-transplant follow-up in the absence of antiviral therapy, were excluded from the analysis, since the primary aim of the study was to verify the impact of gender and donor/recipient gender mismatch on graft outcome in relation to HCV graft infection. Thus, for the purpose of this study, only the 604 anti-HCV positive patients that were also HCV-RNA positive in serum at LT were considered (Fig. 1).

2.3. Outcome measures

The main outcome measure was graft survival.

The secondary outcome measure was graft loss associated with severe recurrent HCV disease, defined as graft loss from complications of advanced liver disease (i.e. variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, sepsis) in the setting of documented advanced fibrosis or cirrhosis.